mL) and ether (20 mL) was added dropwise a solution of **2** (20 mmol) and **3** (20 mmol) in 20 mL of ether at 0 °C over a period of 2 min. After the reaction mixture was kept at room temperature for another 3 h, the usual workup[13] gave **4** in the isolated yields shown in Table I. Further extention of this new joining reaction in organic synthesis will be reported shortly.

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(11) The conditions of electroreduction were as follows: substrate (10 mmol); solvent, dry DMF (40 mL); cathode, Pb; anode, Pt; supporting electrolyte, tetraethylammonium *p*-toluenesulfonate (0.3 M); buffer, solid KH_2PO_4 (3 g); 0.3 A of direct current. The detail of this electroreductive skeletal rearrangement is not clear yet. In the absence of MgX^+, however, compounds of type **4** dissociate into carbonyl compounds and compounds of type **5a** under basic conditions. Thus, the formation of the γ-butyrolactone from **4j** seems to result from the electroreductive coupling of methyl β-phenylthiopropionate with *n*-heptanal since the cathodic solution became basic in the electroreduction. The scope and limitation of this novel electroreductive coupling will be reported elsewhere.
(12) Phenylthiomagnesium iodide was prepared by addition of a solution of thiophenol (20 mmol) in 20 mL of hexane to a solution of methylmagnesium iodide (20 mmol) in ether (20 mL).
(13) The reaction mixture was poured into large excess of an aqueous saturated solution of ammonium chloride, and the organic layer was extracted with ether. Products were isolated by column chromatography.

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Saturation-Transfer Study of the Mechanism of Proton Exchange in Amides

Sir:

The mechanism of proton exchange in amides has been a subject of interest for many years.[1] Two possibilities exist for acid-catalyzed exchange: (1) direct protonation on nitrogen (eq 1)[1a,b] and (2) protonation on oxygen, followed by proton abstraction from nitrogen to generate the imidic acid (eq 2).[1b,c]

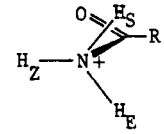
$$H^+ + RCONH_2 \rightleftharpoons RCONH_3^+ \qquad (1)$$

$$\Updownarrow$$

$$RC(OH)=NH_2^+ \rightleftharpoons RC(OH)=NH + H^+ \qquad (2)$$

We have previously concluded,[2] on the basis of indirect evidence, that such exchange in a variety of primary amides occurs via the N-protonation mechanism (eq 1), but with the additional feature that the lifetime of the intermediate, $RCONH_3^+$, is too short to permit rotational equilibration about the C–N single bond. We now present more compelling evidence, based on saturation-transfer experiments, that this mechanism is indeed involved, as well as evidence for the imidic acid mechanism (eq 2) in some cases. Redfield and Waelder[3] have independently obtained similar results for some different amides; their interpretation differs somewhat.

In primary amides, H_E and H_Z (protons respectively trans and cis to oxygen) are diastereotopic, and it is possible to measure each of their exchange rates separately. A distinction between these two mechanisms is provided by comparing rate constants for intermolecular and intramolecular exchange. Let k_{EZ} and k_{ES} be the pseudo-first-order rate constants for exchange from the E site to the Z site and to the solvent site, respectively; other k_{ij}'s are defined analogously. The imidic acid pathway requires that k_{EZ} and k_{ZE} be zero, since the configurational stability[4] of the imidic acids precludes acid-catalyzed intramolecular exchange. In contrast, protonation on nitrogen initially produces[2] the most stable conformer (**1**),



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with H_Z eclipsing oxygen. This conformer can lose H_S or H_E, but loss of H_Z requires rotation about the C–N single bond, whereupon H_Z exchanges with equal probability into the solvent and E sites. Therefore, the N-protonation mechanism requires that $k_{ZS} = k_{ZE}$. The distinction between the imidic acid and N-protonation routes thus depends on whether k_{ZE} is zero or equal to k_{ZS}, respectively. Moreover, in the N-protonation mechanism, to the extent that the lifetime of $RCONH_3^+$ is too short to permit rotational equilibration about the C–N bond, H_E will exchange faster than H_Z. It can be shown that k_{ES}/k_{ZS} or $k_{SE}/k_{SZ} = 1 + k_d/k_r$, where k_d and k_r are first-order rate constants for diffusion-controlled deprotonation[5] and rotation of $RCONH_3^+$, respectively.

Line-shape analysis is too inaccurate for comparing intramolecular exchange with intermolecular exchange. Therefore we have extended[6] the NMR saturation-transfer technique of Forsén and Hoffman[7] to the determination of all six rate constants of a three-site system. The method involves the measurement of not only intensities but also longitudinal relaxation times in Fourier-transform NMR spectra under conditions of selective saturation. These are the same measurements as in NOE (nuclear Overhauser enhancement)[8] studies, except that kinetic transfer of saturation leads to decreases in intensities. The experimental details of this technique are given elsewhere.[6]

We have applied this technique to the proton-exchange kinetics of four primary amides and one imidic ester. In the studies reported here, amides were examined in ethylene glycol, whose high solvent viscosity produces reasonably narrow line widths (8–9 Hz) for H_E and H_Z. Acid-catalyzed exchange was induced by addition of microliter quantities of 0.5 M HCl or concentrated sulfuric acid. Base-catalyzed exchange was induced with phosphate buffers. Nonexchanging samples (acetate buffered) were also examined for each amide. Apparent rate constants measured under nonexchange conditions were subtracted from rate constants measured for acidic or basic samples, to remove contributions from uncatalyzed rotation about the C–N partial double bond and from E–Z cross relaxation.[8] For comparison, water-catalyzed exchange in protonated ethyl acetimidate,[9] $CH_3C(OEt)NH_2^+Cl^-$, was studied in 32% v/v aqueous sulfuric acid. A nonexchanging sample, in 45% v/v aqueous sulfuric acid, served to correct for cross relaxation.

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Table I. Rate Constants for Exchange of E and Z Hydrogens of $RCONH_2$ and One Analogue[a,b]

	acetamide	ethyl acetimidate	acetamide	acrylamide	cyanoacetamide	ethyl oxamate[c]
pH, measured	8.1	(32% H_2SO_4)	1.7	1.7	1.05	0.8
$[H_S]/[H_{E,Z}]$	11.24	10.65	12.06	10.90	27.49	77.9
k_{ES}, s^{-1}	2.67 ± 0.21	1.43 ± 0.09	3.94 ± 0.44	4.63 ± 0.52	7.80 ± 0.70	11.05 ± 0.83
k_{SE}, s^{-1}	0.261 ± 0.020	0.083 ± 0.005	0.356 ± 0.044	0.429 ± 0.054	0.249 ± 0.023	0.123 ± 0.009
k_{ZS}, s^{-1}	1.03 ± 0.10	2.89 ± 0.20	3.26 ± 0.42	3.14 ± 0.46	7.02 ± 0.66	5.54 ± 0.44
k_{SZ}, s^{-1}	0.103 ± 0.010	0.294 ± 0.021	0.301 ± 0.039	0.340 ± 0.050	0.215 ± 0.021	0.059 ± 0.045
k_{EZ}, s^{-1}	0.04 ± 0.08	−0.13 ± 0.12	2.32 ± 0.39	2.51 ± 0.55	1.06 ± 0.26	1.38 ± 0.10
k_{ZE}, s^{-1}	0.01 ± 0.07	−0.01 ± 0.08	2.68 ± 0.43	2.51 ± 0.54	1.29 ± 0.27	1.10 ± 0.08

[a] k_{ij} = pseudo-first-order rate constant for base- or acid-catalyzed exchange form site i to site j (i,j = H_E, H_Z, $H_{solvent}$). [b] Errors are standard deviations determined according to the propagation of errors from the observed standard deviations of repeated saturation-transfer intensities and T_1's. Although all six rate constants are determined independently, the errors are not independent. [c] Assignment of H_E and H_Z by analogy to other amides.

Table I lists sample conditions and rate constants obtained for the compounds studied. To check the reliability of this method, we have first examined base-catalyzed exchange in acetamide, for which there is no mechanistic ambiguity.[2] Since the imidate anions resulting from loss of H_E or H_Z are expected to be configurationally stable,[10] no base-catalyzed E–Z exchange is expected, and this is indeed confirmed by the kinetic data: k_{EZ} and k_{ZE} are zero, within experimental error. Moreover, we note that H_E exchanges faster, in accord with previous line-broadening measurements,[2] and forward and reverse rates are equal ($k_{ES}[E] = k_{SE}[S]$, etc.), within experimental error, as required by equilibrium. Thus we may have confidence in this saturation-transfer method.

Water-catalyzed proton exchange in protonated ethyl acetimidate serves as a model for the imidic acid route. Table I shows that there is no E–Z exchange, and that H_Z exchanges faster than H_E, as expected based on the known stabilities of imidic esters.[11]

Kinetic data for acid-catalyzed exchange of acetamide and acrylamide demonstrate that k_{ZE} differs from k_{ZS} by <1 standard deviation. (The discrepancies between forward and reverse rates provide a further measure of the reliability of these values.) We therefore conclude that exchange in these amides proceeds predominantly via the N-protonation route, although we cannot exclude a small fraction of exchange via the imidic acid. Moreover, for both these amides, k_{ES} and k_{SE} are significantly greater than k_{ZS} and k_{SZ}, respectively. This verifies our previous result,[2] which depended on small differences in line widths. We again interpret this in terms of preferential formation of conformer **1**, which is such a strong acid that deprotonation is competitive with rotation about the C–N single bond.

Table I also lists data for acid-catalyzed exchange of cyanoacetamide and ethyl oxamate ($EtOCOCONH_2$). For both amides, k_{ZE} is considerably smaller than k_{ZS}, indicating that exchange occurs predominantly through the imidic acid route. Some exchange via N-protonation is nevertheless occurring, since k_{ZE} and k_{EZ} are nonzero. For H_Z, the fraction of solvent exchange occurring via the latter pathway is simply k_{ZE}/k_{ZS}, or 18 and 20% for cyanoacetamide and ethyl oxamate, respectively. For H_E, the N-protonation path represents at least 14 and 12%, respectively, of the total intermolecular exchange.

The results obtained for the various amides may be rationalized by noting that the ratio of exchange via the N-protonation and imidic acid pathways can be shown to be proportional to K_T^+/K_a^1, K_T/K_a^N, or $K_TK_T^+/K_a^O$, where K_T^+ and K_T are tautomeric equilibrium constants for the ratio of N- to O-protonated amide and the ratio of neutral amide to imidic acid, respectively, and where K_a^1, K_a^O, and K_a^N are acidity constants for proton loss from nitrogen and oxygen in the O-protonated amide and from nitrogen in the N-protonated amide. To the extent that the tautomeric equilibrium constants are less sensitive to substitution than the acidity constants are, we may expect that electron-withdrawing groups, such as $NCCH_2$– and EtOOC–, which increase K_a^1, K_a^O, and K_a^N, should favor the imidic acid mechanism, whereas electron-donating groups such as methyl and vinyl should favor the N-protonation pathway. Qualitatively this is reasonable, since the transition state for the imidic acid mechanism resembles the uncharged imidic acid, whereas the transition state for the N-protonation mechanism resembles the cation, $RCONH_3^+$. Thus cyanoacetamide, with a pK_a^O of −3.7,[12] is considerably more acidic than either acetamide ($pK_a^O = -0.9$)[12] or acrylamide ($pK_a^O = -0.3$),[13] and exchanges mostly through the imidic acid route. Likewise, ethyl carbethoxyimidate, $EtOCOC(OEt)NH_2^+$, which serves as a model for O-protonated ethyl oxamate, has a $pK_a^1 < 5.2$[13] and is considerably more acidic than ethyl acetimidate ($pK_a^1 = 7.6$),[13] which serves as a model for O-protonated acetamide. Thus ethyl oxamate may also be expected to be more likely to exchange via the imidic acid route.

We therefore conclude that "typical" primary amides undergo acid-catalyzed exchange predominantly via the N-protonation mechanism, as evidenced by a near equality of k_{ZE} and k_{ZS}. In contrast, primary amides with electron-withdrawing substituents exchange predominantly via the imidic acid, as evidenced by intermolecular exchange accompanied by little acid-catalyzed intramolecular exchange.

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